

# PATENT ABSTRACTS OF JAPAN

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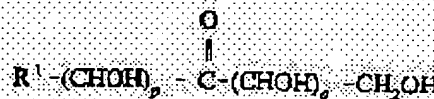
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## (54) COLLAGEN-BASED MATRIX

(57)Abstract:

**PROBLEM TO BE SOLVED:** To obtain a collagen-based matrix suitable for use in the instruments capable of being intracorporeally embedded such as membranes or tubes for the regeneration of inducing tissues by reacting collagen with a reducing sugar under specified conditions.

**SOLUTION:** This collagen-based matrix is obtained by reacting collagen with a reducing sugar under conditions in which the molecules and the fibrils of collagen crosslink with each other. This collagen-based matrix contains collagen fibrils in which the molecules or the fine fibers are crosslinked to each other with a crosslinking agent and the reducing sugar or its derivative of such a kind that the crosslinking agent can exist in the form of aldehyde or ketone in the aqueous solution. This crosslinking agent may be a compound represented by formula I or II (wherein, R1 is H, a lower alkyl, an alkylene, an



amino acid, a peptide, a saccharide, a purine base, a pyrimidine base, phosphorylated purine or a pyrimido base; (n) is 2-9; (p) and (q) are each 0-8;  $p+q \geq 2$ ; and  $p+q \leq 8$ ).

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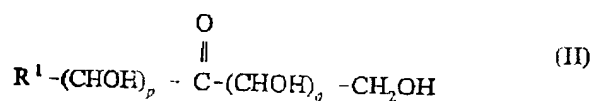
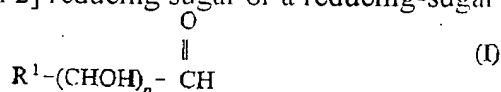
CLAIMS

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## [Claim(s)]

[Claim 1] The collagen matrix characterized by including the reducing sugar or the reducing-sugar derivative of a class with which a cross linking agent can exist in the state of an aldehyde or a ketone in a water solution including the collagen fibril by which the bridge is mutually constructed over a molecule or thin fiber by the cross linking agent.

[Claim 2] reducing sugar or a reducing-sugar derivative -- the degree type I or II: -- [Formula 1]



It is the collagen matrix according to claim 1 which is the compound shown by one of [the R1 is H, low-grade alkyl or alkylene, amino acid, a peptide, a saccharide, a pudding or a pyrimidine base, a phosphorylation pudding, or a pyrimide base among a formula, n is the integer of 2-9, p and q are the integers of 0-8 independently, respectively, however the sum total is at least 2 and p and q are eight or less].

[Claim 3] Equipment including claim 1 or the matrix of any one publication of two in which implant is possible.

[Claim 4] Equipment according to claim 3 which is a film obstruction for induction (guided) anagenesis.

[Claim 5] The matrix which contains the 2nd component which is osteocalcin or vitronectin in the 1st component list chosen from the group which consists of lime occification, a deproteinization bone, and synthetic hydroxyapatite.

[Claim 6] The matrix containing a heat treatment decalcification bone.

[Claim 7] The kit for using by the induction anagenesis containing the anagenesis induction film according to claim 4 and space maintenance material.

[Claim 8] The manufacturing method of a collagen matrix including making a collagen react under the conditions over which the fibril of reducing sugar, a molecule, and a collagen constructs a bridge mutually.

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DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to equipment including a new collagen-base matrix and this matrix. Such a specific example of equipment is a useful collagen-base sheet in induction (guided) anagenesis (GTR), and calls it the "GTR film" on these specifications.

[0002] The specific application of the GTR film of this invention is an application for the induction anagenesis of a root-of-tooth organization in a dentist way.

[0003] This invention relates also to the manufacturing method of a matrix.

[0004]

[Description of the Prior Art] Induction anagenesis is a surgical operation method aiming at restoring or reproducing the gestalt and function of the organization or organ destroyed by the disease or the trauma. In the case of anagenesis, the organization to reincarnate has to do reaggregation (repopulate) to the destroyed healthy tissue having occupied before in the same part and space. Furthermore, it must be the morphological and cooperative process between the various neoformation in a playback part in which the reaggregation of the risked part and the continuing differentiation of a reaggregation cell have order in order to restore a functional relationship.

[0005] The approach of GTR aims at making possible cooperative reaggregation with the risked order of a part by rebirth of an organization. An obstruction is placed among the organizations which may intervene between neoformation and a renewal process for this purpose. Reaggregation of the risked part is done by the right organization, and an obstruction is held in a proper place until neoformation reaches maturation.

[0006] The film obstruction is used for GTR of a rebirth of the current and root-of-tooth organization destroyed [ in / mainly / the dentist way ] by the root-of-tooth disease or the trauma. Two kinds of film of the film made from the film and resolvability ingredient which were generally made from the nondegradable ingredient is used.

[0007] A collagen is the proteinic whole family who has the fully determined triple-helix configuration. Most collagen I-beams exist in these protein, and about 80% of the protein of the about 25% and connective tissue of bodily protein is constituted. The polymerization of the collagen I-beam is carried out, and it forms the aggregate of fiber and a bundle. The collagen is always reconfigured by decomposition and composition in the body. It is decomposed by only specific enzyme-collagenase and a collagen I-beam is resistance also to which nonspecific proteolysis.

[0008] A collagen is a weak antigen and the antigenic most is in the non-whorl end of a molecule. These ends are removable with enzymes, such as a pepsin. Antigenic [ the / weak ] and the relative resistance over the decomposition make the collagen the candidate who was excellent as a construction ingredient of the equipment in which implant is possible.

[0009] The molecule solution of an I-beam collagen can be prepared from the abundant connective tissue of this protein, subsequently to fibril can carry out reaggregation of the molecule collagen, and, subsequently can form a collagen matrix combining it. A collagen matrix can be fabricated within a test

tube and can be used as the equipment in which much implants are possible, for example, a collagen sheet, collagen tubing, etc.

[0010] When used for formation of the equipment in which implant is possible, a collagen matrix must hold the integrity for a long period of time. The resistance over decomposition of collagen fibril can be raised by making the number of intermolecular bridge formation increase. It has been used for achievement of processing of several sorts of reagents, such as aldehyde fixing fluid and imide, radiation irradiation, etc. of this purpose. The main faults of such processing are that extent of toxicity and bridge formation is correctly uncontrollable.

[0011]

[Problem(s) to be Solved by the Invention] The purpose of this invention is offer of the collagen matrix for which it was suitable in order to use with the equipment in which implants, such as film for induction anagenesis or tubing, are possible.

[0012] Another purpose of this invention is offer of the manufacturing method of such a matrix.

[0013] Still more nearly another purpose of this invention is offer of the kit which contains a useful component in an induction organization reclaiming process.

[0014] Still more nearly another purpose of this invention is offer of the approach of induction anagenesis (GTR).

[0015] still more nearly another purpose of this invention -- GTR -- it is offer of the space maintenance material for using by law.

[0016]

[Means for Solving the Problem] When following this invention, it was found out using constructing a bridge in a collagen by making a collagen react with reducing sugar that a collagen can be made into resistance to collagenolysis (collagenolytic degradation). In this way, according to this invention, it can be kept substantial in a body for a long period of time being damaged [ no ], and a bridge formation collagen matrix useful as a construction ingredient of various collagen-base implant possible equipments is offered.

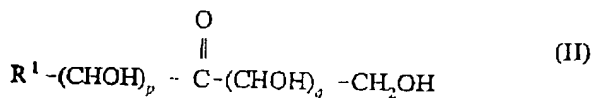
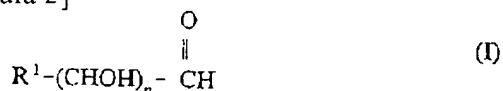
[0017] This invention offers the collagen matrix in which a cross linking agent contains reducing sugar or a reducing-sugar derivative including the collagen fibril by which the bridge is mutually constructed over the molecule or thin fiber by the cross linking agent according to the 1st description.

[0018] Further, this invention makes a collagen react with a reducing agent, and offers the manufacturing method of the collagen matrix in which the fibril of a collagen includes that a bridge is constructed mutually by that cause. It is desirable to dehydrate a collagen matrix for example, in an alcoholic solution following manufacture, and to carry out critical point desiccation subsequently.

[0019] This cross linking agent can be a monosaccharide derivative with which an aldehyde monosaccharide or alpha-carbon exists in the state of an aldehyde or a ketone in a water solution.

[0020] This cross linking agent is the degree type I or II: [0021].

[Formula 2]



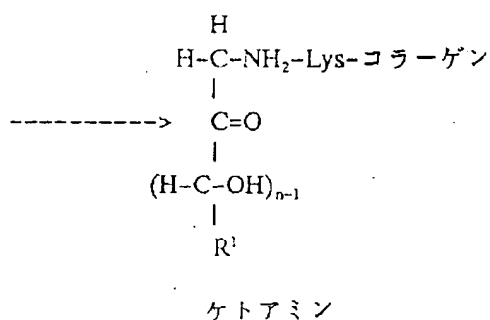
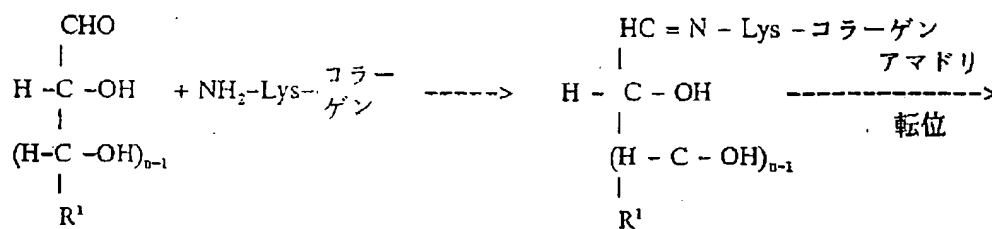
[0022] It can be the compound shown by one of [the R1 is H, low-grade alkyl or alkylene, amino acid, a peptide, a saccharide, a pudding or a pyrimidine base, a phosphorylation pudding, or a pyrimide base among a formula, n is the integer of 2-9, p and q are the integers of 0-8 independently, respectively, however the sum total is at least 2 and p and q are eight or less].

[0023] Reducing sugar can form alpha or epsilon amino group, and the Schiff base of amino acid of a collagen molecule. A Schiff base is : [0024] which performs an Amadori rearrangement by the

following reaction formulae, and forms a keto amine product.

[Formula 3]

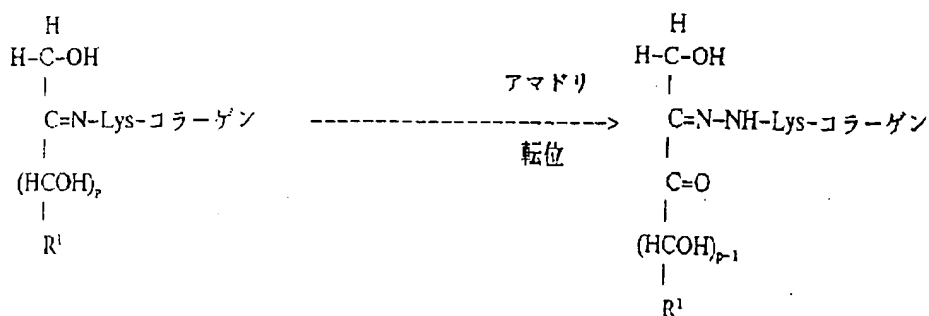
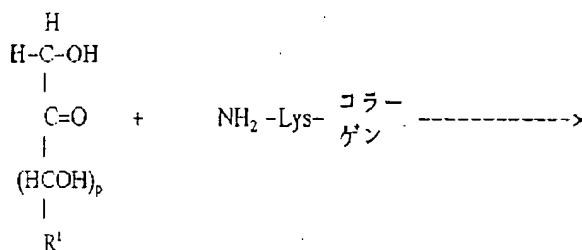
a. アルデヒド糖



[0025]

[Formula 4]

b. ケトン糖

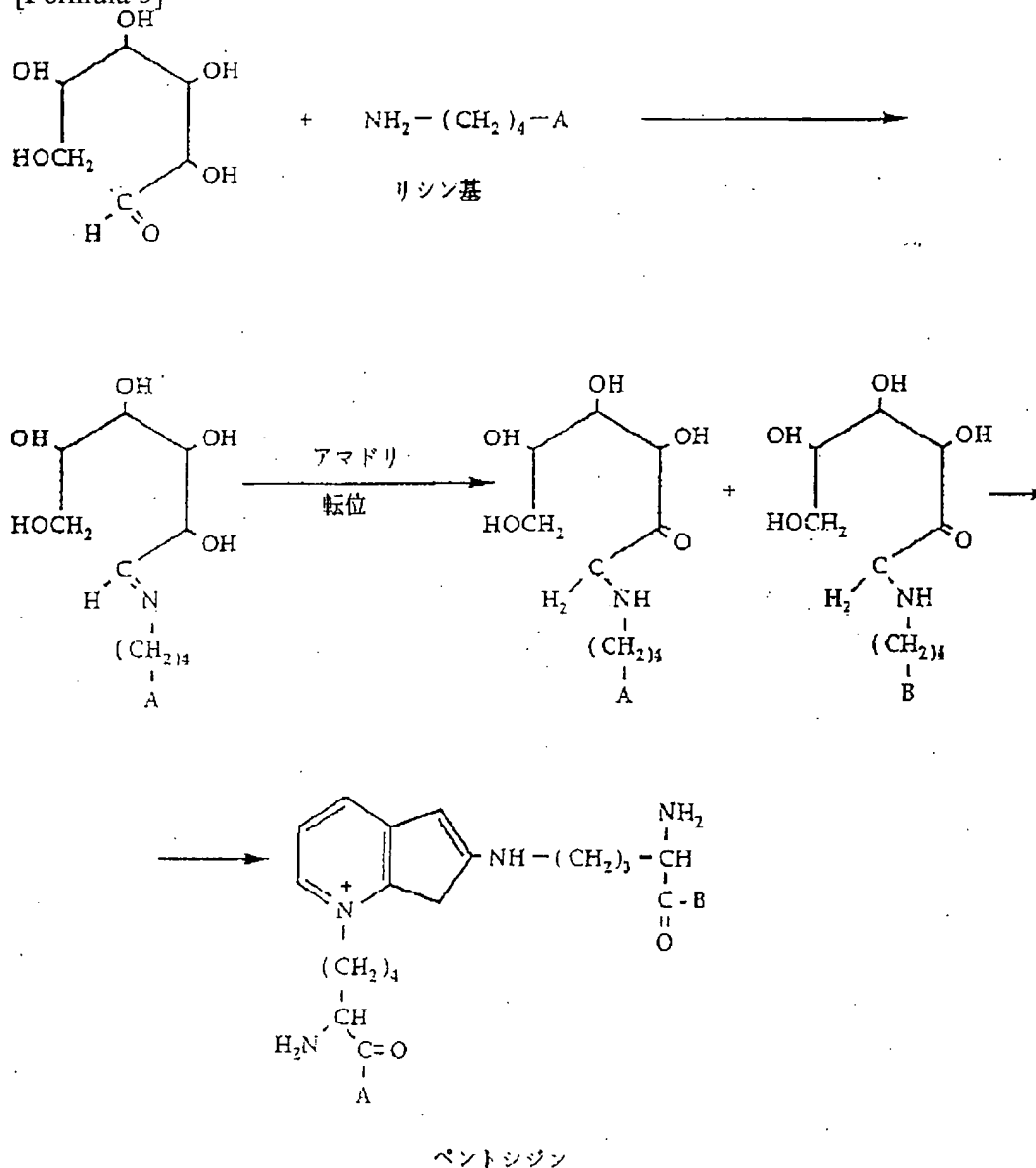


[0026] Subsequently, two adjoining keto amine radicals form between the molecules which condensed

and were suitable, or intramolecular branching.

[0027] : which can form the stable bridge formation through a pentosidine (pentosidine) radical by the following reaction formulae when a cross linking agent is a ribose (in a degree type, "A" shows the 1st collagen molecule and "B" shows the 2nd collagen molecule) [0028]

[Formula 5]



[0029] The example of this reducing agent is a glycerose, a threose, an erythrose, lyxose, a xylose, arabinose, a ribose, allose, altrose, a glucose, a mannose, growth, idose, a galactose, a talose or other dioses, triose, tetrose, a pentose, a hexose, SEPUTOSU, octose, NANOSU, or decose.

[0030] The catabolic rate of the collagen matrix in the living body is controllable by extent of bridge formation between the collagen molecules in a matrix. The concentration of the sugar between manufactures of a matrix, temperature, and a collagen can control this by the die length of the time amount exposed to sugar shortly.

[0031] A matrix can contain the various drugs which have a curative effect of a certain kind, and it is fixed by this saccharide in a matrix. When a matrix is in an original location, these drugs are gradually emitted, while a matrix decomposes gradually. An anti-microorganism agent, an anti-inflammatory agent, the factor that has anagenesis inductivity are contained in these drugs.

[0032] The examples of an anti-microorganism agent are antimicrobials, such as antibiotics, such as

penicillin, cephalosporin, a tetracycline, streptomycin, and gentamycin, a sulfonamide, and miconazole. [0033] The example of an anti-inflammatory agent is cortisone, its synthetic derivative, or one of synthetic antiinflammatory drugs.

[0034] The examples of the factor which has organization inductivity are differentiators, such as growth factors, such as a fibroblast growth factor, a platelet derived growth factor, a transforming growth factor, a cement growth factor, and an insulin-like growth factor, and bone morphogenesis protein, and adhesin (attachment factor) (even if these use bridge formation by using the natural capacity combined with the collagen according to a saccharide, they are combinable with a matrix).

[0035] The collagen matrix of this invention is useful because of a nerve or the revascularization to manufacture of the sheet which acts as a film obstruction for GTR, and two or more implant equipments containing collagen-base tubing.

[0036] The obstruction film of this invention is range whose thickness is 0.05mm - 2mm typically. A membranous dimension is the range of 2, or more than it about 0.5cm 2-400cm.

[0037] The collagen film of this invention is resistance also to which nonspecific proteolysis. They are decomposed at a rate controllable by the amount of bridge formation as they are the above and were already pointed out by collagenase.

[0038] If one embodiment of this invention is followed, a collagen matrix can be used combining a space-maintenance ingredient ("space maintenance material"). Space maintenance material is used in some approaches, in order for a playback cell to move and to hold the space which can carry out reaggregation. For example, in some when a neoplasm is started from a bone, such space happens automatically. For example, in others, such as the various roots of tooth or a bony failure, such space cannot be used. In such a case, it is required between an obstruction and neoformation to insert a packing material. The examples of space maintenance material are osteocalcin other than (i) HIARURONAN (hyaluronic acid), (ii) mineralization freeze-drying bone, a deproteinization (iii) bone, (iv) composition hydroxyapatite, and the thing mentioned by (v) (ii) - (iv) or the thick crystalline ingredient of vitronectin, and (vi) heat treatment decalcification bone (the bone origin matter of (ii) and (iii) (vi) has the desirable thing of the Homo sapiens origin). The combination of the combination of one of the above-mentioned space maintenance material especially HIARURONAN, one, or other space maintenance material beyond it is also possible.

[0039] HIARURONAN with desirable being given with the gestalt probably freeze-dried is a polysaccharide which consists of glucuronic acid and the repeat unit of N-acetyl glucosamine. It has the molecular weight of the range of thousands - 1 million dalton of numbers depending on the source of an extract. In the organization under growth and recovery, it is automatically discovered, and HIARURONAN has the capacity which combines a lot of water. These properties are enabled to use HIARURONAN as space maintenance material combining the film of this invention in GTR.

[0040] It is thought that an OSUTE okra strike (bone resorption cell) is induced the front face which osteocalcin and vitronectin [osteocalcin are bone protein, combined with hydroxyapatite (bony mineral component) lime occification, a deproteinization bone (it is the natural hydroxyapatite manufactured by ashing a bone at 700 degrees C), or synthetic hydroxyapatite, and was calcified. BICHIRONE cutin is adhesion protein and it is thought that it is new to use adhesion of the OSUTE okra strike to the front face of the calcified bone combining] made easy, and the supplement of the OSUTE okra strike in a recovery part is strengthened. This strengthens the resorption of these space maintenance material shortly, and makes the permutation by neoformation easy.

[0041] Heat treatment of a decalcification bone (for example, freeze drying) denatures the collagen nature component of a bone matrix, and it is made for a bone matrix to decompose it by nonspecific proteolysis. This strengthens decomposition of space maintenance material shortly, and makes the permutation by neoformation easy. Especially heat treatment preparation such for this application is new.

[0042] Are dependent on the dimension, gestalt, and location of a playback part. Space maintenance material for various applications One sort or the above-mentioned \*\* bacteria agent beyond it, The matter for being able to make it thick by the anti-inflammatory agent and the organization inducer,



and/or helping maintenance of the form of a space maintenance material matrix, For example, a collagen, a fibrin, fibronectin, osteonectin, It can be made thick by the matrix protein and/or the heparin sulfuric acid, the dermatan sulfate, the chondroitin sulfate, the keratan sulfate, and other many beyond one sort chosen from the group which consists of osteopontin, TENASHIN, and TRON BOSHONJIN, or it.

[0043] These which are offered by this invention are the above-mentioned new space maintenance material.

[0044] This invention also offers the kit for using by GTR containing the collagen film of this invention. When the embodiment of this invention is followed, a kit also contains space maintenance material. The collagen film and HIARURONAN can contain the above-mentioned additive beyond one sort or it.

[0045] This invention is further illustrated according to explaining a specific embodiment below and the example which indicates the experiment of shoes conducted within the limit of this invention, and an attached drawing is also mentioned.

[0046]

[Detailed explanation of a specific embodiment]

The manufacture I-beam collagen of the collagen film can be obtained from the skin of a cow, a tendon, a placenta, or people's placenta by pepsin-ization as itself known. The molecule solution (1-10mg/(ml)) of a purification pepsin-ized I-beam collagen is dissolved into the acetic acid of 0.05M, and it holds at 4 degrees C, mixes with NaOH of 0.1M, pours into the mold which was subsequently suitable, and incubates at the temperature of the range of 20-37 degrees C for 24 hours. Subsequently the matrix manufactured is compressed at a piston, and water is pressed out until the film of required thickness is obtained by that cause. subsequently, the resistance which needs the film [ as opposed to zymolysis for the film ] in the solution (it has the concentration of the range of 0.05M-1M) of a ribose -- depending -- 6 hours - 24 days -- being certain -- it is -- yes -- the case of shoes -- more than it -- period incubation is carried out.

[0047] If, a ribose solution can be made thick with drugs, such as a \*\* bacteria agent and antimicrobial, an antiinflammatory drug, a mitogen, and a differentiation agent.

[0048] Required modification can be added and equipments other than film, such as tubing, can be manufactured from a collagen matrix by the similar approach.

[0049] Subsequently, collagen equipment is dried and it sterilizes. For this purpose, collagen equipment is among air or can be dehydrated by being immersed in an alcoholic solution (30% - 100%).

Subsequently critical point desiccation of the dehydrated equipment is carried out in a critical point drier by the pressure of about 41 degrees C and about 80-90 bars for example, in a carbon dioxide (CO2) or the gas of others, such as Freon. This approach sterilized equipment, they were dried completely, and it was found out that it is effective in extending that shelf life. This approach does not affect the resistance over the collagenolysis of these collagen equipments. Still such an approach saves the three-dimensions-gestalt of equipment.

[0050] In order to manufacture the film which has the part decomposed with different catabolic rate, the part designed so that it might be more equal to prolonged decomposition is contacted in a ribose solution. The whole film is incubated with a ribose solution after required time amount.

[0051] For example, the part of the film of the rectangle which adjoins one of the two shorter sides is dipped in the time amount ribose solution which was able to be decided beforehand, holding :film which can take the following approaches in the atmospheric air whose humidity is 100%, in order to manufacture the film of the rectangle which has the inclination of catabolic rate in the direction of [ from one rectangular shorter side ] the opposite side (it has catabolic rate with one high shorter side, and other sides have low catabolic rate). The part which adjoins after that is immersed gradually the time on which it decided as the ribose solution beforehand. It is the shortest time amount that the maximum end remains in a ribose solution in this way, and it becomes the part which is the easiest to receive decomposition in this way.

[0052] It dissolves into the water solution as for which the above-mentioned factor made thick HIARURONAN obtained from the space maintenance (material a) freeze-drying HIARURONAN

people, the cow, or the source of birds at one or which does not make it thick, and, subsequently freeze-dries. It was found out that it is suitable in order for thick freeze-drying HIARURONAN by which the entheses was carried out to the skin to absorb and swell water according to this invention, to become gelatin nature workability and to be useful to the purpose of space maintenance material in this way. [0053] (b) Mix the mineralization freezing-desiccation bone of a bone formation object or 1g of hydroxyapatite products, a deproteinization bone, or synthetic hydroxyapatite with the solution containing a maximum of 15mg osteocalcin and/or 10mg vitronectin, and, subsequently freeze-dry mixture.

[0054] the particle of a decalcification freeze-drying bone -- the inside of a desiccation ambient atmosphere or a caustic alkali solution -- the temperature of the range of 50 degrees C - 100 degrees C -- the time amount of the range for 5 minutes - 240 minutes -- it heats. When heat-treating in a water solution, a decalcification bone is again freeze-dried following heat treatment. This invention was followed and it was found out that proportionality is between the rate of decomposition of the decalcification bone by the trypsin in a test tube and the temperature of heat.

[0055] (c) the ingredient of the above [ the space maintenance material used combining the use collagen obstruction of the space maintenance material together with a collagen ] -- respectively -- or consist of those combination. For example, space maintenance material is a heat treatment decalcification freeze-drying bone and/or osteocalcin. It can consist of the freeze-drying matrix of HIARURONAN containing the particle of the deproteinization bone processed by vitronectin. For manufacture of such an ingredient, a heat treatment decalcification freeze-drying bone and a thick deproteinization bone are mixed with the solution of HIARURONAN, and, subsequently mixture is freeze-dried.

[0056]

[Example]

Example I: It incubated in the PBS solution which contains a ribose or does not contain the collagen fibril by which the radioactive indicator was carried out by the test tube internal division solution tritium. The amount of the collagen fibril in a solution was 3microg/ml, and the concentration of a ribose was 0.2M. The incubation of the collagen fibril in a solution was performed at the temperature of 37 degrees C, and was the period of the range on one - the 16th.

[0057] the collagen matrix formed in this way following this incubation -- collagenase -- 1 (weight 1:10 collagens : collagenase) and 2 -- or it incubated for 4 hours. Following this incubation, centrifugal [ of the solution ] was carried out and the amount of residual radioactivity which consists of a next collagen matrix was determined. The result of a radioactive count is shown in drawing 1 . After processing by collagenase following the incubation of the collagen fibril in PBS, the radioactivity ((b) in drawing 1 ) which remains in a matrix was 40% or less, as it understood. On the other hand, the radioactive amount ( drawing 1 ) which remains in the matrix formed after carrying out a prolonged incubation from six days in a ribose solution was about 85 - 90%.

[0058] This shows clearly that resistance was much higher than other matrices to specific decomposition according [ the collagen matrix formed after the incubation in the ribose solution over which a collagen molecule is made to construct a bridge mutually ] to collagenase.

[0059] Example II: The collagen matrix containing (Biodegradation a) radioactivity indicator collagen of 100micro of each g was processed by the ribose for 1, 3, and nine days by the approach of a publication, and the similar approach in the example 1. Subsequently, implant of the matrix was carried out through the standard hole (about 1x3mm) made by the thigh of a rat. The radioactive amount left behind to each hole at the sacrifice of the animal as of 21 days after [ 0, 7, and 14 ] implant was determined. Seven animals were sacrificed at each time.

[0060] Catabolic rate was able to be determined by measuring radioactivity and comparing with the radioactivity which exists in the collagen matrix which had it manufactured. It showed that it decomposed about the sample which the sample processed by 1, 3, and the ribose during nine days at 3% per day, 2%, and 0.5% of rate, respectively.

[0061] (b) After processing the film with a dimension of about 0.5x1cm manufactured for nine days by the ribose as above-mentioned passage [ in an example 1 ], the entheses was carried out to the bottom of

the gum of a dog and a man. Using the histological approach, although the film decomposes completely in a dog, this thing was found out for about four months. Using the reentering method (re-entry procedure) performed in people, the film decomposed completely, and although it disappears, this thing was measured for about six months. The fact that the film is held in an original location such for a long period of time makes it easy to use it for induction anagenesis.

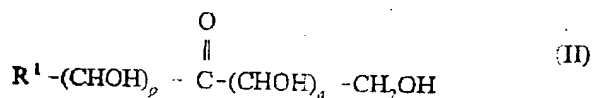
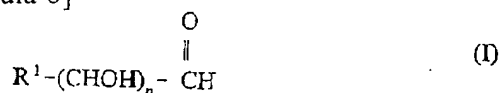
[0062] Example III: It dealt with the experimental root-of-tooth deficit made at the cheek side of the premolar of a dog using the collagen film manufactured as the animal experiment above. The histological trial of the treatment part four months after taking a measure by the collagen film clarified 90% of playback of a deficit dimension.

[0063] The main description and main mode of this invention are as follows.

[0064] 1. Collagen matrix characterized by including reducing sugar or reducing-sugar derivative of class with which cross linking agent can exist in the state of aldehyde or ketone in water solution including collagen fibril by which bridge is mutually constructed over molecule or microfibril by cross linking agent.

[0065] 2. Reducing Sugar or Reducing-Sugar Derivative is Degree Type I or II: [0066].

[Formula 6]



[0067] It is a collagen matrix given in the 1st above-mentioned term which is the compound shown by one of [the R<sup>1</sup> is H, low-grade alkyl or alkylene, amino acid, a peptide, a saccharide, a pudding or a pyrimidine base, a phosphorylation pudding, or a pyrimide base among a formula, n is the integer of 2-9, p and q are the integers of 0-8 independently, respectively, however the sum total is at least 2 and p and q are eight or less].

[0068] 3. Collagen matrix given in the 2nd above-mentioned term whose reducing sugar are diose, triose, tetrose, pentose, hexose, SEPUTOSU, octose, NANOSU, or decose.

[0069] 4. Collagen matrix given in the 3rd above-mentioned term which is member as whom reducing sugar are chosen from group which consists of glycerose, threose, erythrose, lyxose, xylose, arabinose, ribose, allose, altrose, glucose, mannose, growth, idose, galactose, and talose.

[0070] The collagen matrix of any one publication of one to 4 above-mentioned term by which these drugs or a factor is being fixed in the matrix also including 5.1 sorts, the anti-microorganism agent beyond it, the anti-inflammatory agent, or the factor that has organization inductivity.

[0071] 6. Equipment including matrix of any one publication of one to 5 above-mentioned term in which implant is possible.

[0072] 7. Equipment given in the 6th above-mentioned term which is film obstruction for induction anagenesis.

[0073] 8. Matrix containing the 2nd component which is the 1st component and osteocalcin, or vitronectin chosen from group which consists of lime occification, deproteinization bone, and synthetic hydroxyapatite.

[0074] 9. Matrix containing heat treatment decalcification bone.

[0075] 10. The above 8 for using as space maintenance material in induction anagenesis, or a matrix given in the 9th term.

[0076] 11. The kit for using by the induction anagenesis which contains the anagenesis induction film and space maintenance material of a publication in the 7th above-mentioned term.

[0077] 12. A kit given in the 11th above-mentioned term chosen from the group to which space maintenance material changes from lime occification, a deproteinization bone, synthetic hydroxyapatite,

and a decalcification heat treatment bone.

[0078] 13. The manufacturing method of a collagen matrix including making a collagen react under the conditions over which the fibril of reducing sugar, a molecule, and a collagen constructs a bridge mutually.

[0079] 14. An approach given in the 9th above-mentioned term which carries out critical point desiccation of the collagen matrix which dehydrated the collagen matrix and was subsequently dehydrated.

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[Translation done.]